

illness, deteriorated rapidly, and died. Necropsy was not performed. We do not feel that she died of MDR-TB.

Improved survival for patients with MDR-TB and AIDS may be achievable with early diagnosis and treatment.^{4,5} However, the optimum long-term arrangement for patients with MDR-TB and AIDS is unknown. Although stabilisation of such patients may be possible, cure may not be. Because many patients remain intermittently smear and culture positive for months, return to their former residences, if they house other HIV-infected persons, or to a congregate setting, is precluded. Our patients spent 594 days in respiratory isolation. The cost of the hospital admission exceeded \$445 000; the cost to the patient in loss of dignity and hope cannot be measured. Public health policy should be developed to include alternative sites for the long-term care of survivors of AIDS and MDR-TB.

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Intravenous fluids and paraesthesia

SIR—Emergency admission with a low intestinal obstruction gave me a patient's view of a hospital. I told the tea ladies while recovering from surgery that their tea, coffee, cocoa, and water were so unpalatable as to be virtually undrinkable, to which they replied that all patients on intravenous fluids lost their sense of taste but that it would return three days after my drip was withdrawn. I had assumed that it was the effect of the anaesthetic and operation—as did the nurses. The catering staff assured me that it was only patients on drips who reacted thus, even those who had not had anaesthesia.

52 hours after withdrawal of intravenous fluids my parosmia ended and the ward no longer had a neglected-laundry odour. I suggest that at a certain point the intravenous saline alters the osmotic balance in the oral cavity and nasopharynx, affecting the taste buds and olfactory end organs and thus causing reversible paraesthesia and parosmia. Since few seem to be aware of this physiological reaction to intravenous fluids (despite the fact that such fluids have been used for about a century) it should be more widely reported.

Intravenous-fluid paraesthesia has pertinent implications. In maternity work, bonding between baby and mother could be damaged if either is given intravenous fluids. In puerperal depression it might add to distress. It can affect patients being treated for bulimia and anorexia. The reaction might be used when treating tobacco addicts, to help them reject their cigar, cigarette, or pipe. It could account for the ending

of their addiction by smokers who undergo surgery. Perhaps it explains criticism of hospital catering.

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Protection against Alzheimer's disease with apoE ϵ 2

SIR—An association between the apolipoprotein ϵ 4 allele and Alzheimer's disease (AD) has been observed in many studies.¹ Increased dosage of the ϵ 4 allele appears to decrease the age of onset of AD¹ and may increase the β -amyloid plaque burden in AD brains² which suggest the association has biological importance. There is some evidence for a negative association, or protective effect, of the ϵ 2 allele in sporadic cases of AD.¹ We report further evidence for this effect.

93 patients with sporadic AD (mean [SD] age 75 [8]) and 67 normal controls from the same ethnic background (mean age 77 [10]) were recruited through the patient registry of the Washington University Alzheimer's Disease Research Center. Individuals were genotyped at the apoE locus with a standard method. We found an increase in ϵ 4 allele frequency in patients compared with controls ($\chi^2=7.75$, 1 degree of freedom, one-tailed $p=0.0027$) and a decrease in ϵ 2 allele frequency (Fisher's exact test, one-tailed $p=0.0048$) whereas the decreased frequency of ϵ 3 in the patient group was not significant. Allele ϵ 2 conferred a strong protective effect in our sample, with the odds ratio for AD for subjects possessing this allele being 0.08 (95% CI 0.01-0.69). In contrast, the protective effect of the ϵ 3 allele was less marked (odds ratio for possessing at least one ϵ 3 allele 0.16), and not significant (95% CI 0.18-1.37).

The strength and specificity of the effect of the ϵ 2 allele suggest that the cause is not simply the absence of an ϵ 4 allele but that the ϵ 2 mutation confers protection against AD when compared with the ancestral apoE ϵ 3 allele. The observation of opposite effects on the risk for AD by two different alleles at the apoE locus provides additional support for the direct involvement of apoE in AD pathogenesis.

The pathogenic mechanism of apoE in AD is not fully understood but may be mediated by binding to soluble β -amyloid.⁴ The ϵ 4 allele has been shown in vitro to have a higher binding affinity for β -amyloid than ϵ 3. If this explains the predisposing effect of the ϵ 4 isoform then we would expect apoE ϵ 2 to have a lower affinity for β -amyloid. We would also predict that individuals with ϵ 2/ ϵ 3 and ϵ 2/ ϵ 2 genotypes would have lower β -amyloid plaque densities than either ϵ 3 homozygotes or individuals with an apoE ϵ 4 allele. Since AD is an important cause of morbidity in the elderly, the protective effect of apoE ϵ 2 on risk for AD may explain the recently reported positive association of apoE ϵ 2 with

Genotype	Controls (n=67)	Sporadic AD (n=93)
ϵ 2/ ϵ 2	0	0
ϵ 2/ ϵ 3	8	1
ϵ 2/ ϵ 4	0	0
ϵ 3/ ϵ 3	39	46
ϵ 3/ ϵ 4	19	38
ϵ 4/ ϵ 4	1	8
Allele frequency		
ϵ 2	0.060	0.005
ϵ 3	0.783	0.705
ϵ 4	0.157	0.290

Table: apoE allele frequencies in sporadic AD cases and non-demented controls

human longevity.¹ Understanding the role of apoE ϵ 2 in protecting against the risk of AD should contribute greatly toward the development of treatments and preventive strategies for AD.

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Fulminant hepatitis C virus infection

SIR—Transfusion-associated hepatitis C virus (HCV) infections have been reduced with the introduction of serological testing for HCV. However, even second-generation HCV assays enabling the detection of structural and nonstructural viral proteins lack the sensitivity to detect viraemia in all cases.¹ Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analogue that has been shown to be effective in the treatment of hairy-cell leukaemia with complete remission rates between 75% and 85%^{2,3} and few side-effects. Little is known about possible interactions with liver disease, but an increase in alanine aminotransferase (ALT) has not been reported.

We report a 51-year-old female patient with hairy-cell leukaemia who received three units of packed red cells 18 days before initiation of treatment with cladribine (0.1 mg/kg daily). Liver function tests were normal before treatment. Treatment, however, had to be stopped after 3 days because jaundice and grade 1 encephalopathy developed. On day 10, ALT concentrations peaked at sixty times normal, encephalopathy progressed to grade 2, and prothrombin fell to 25% (normal >70%). By day 25, ALT had returned to normal and the patient subsequently made a complete recovery.

Cladribine caused a 7-day episode of neutropaenia and rapid clearing of hairy cells from peripheral blood within a week. A substantial fall in ALT values followed the drop in peripheral helper (CD4) and suppressor (CD8) T cells with a delay of 6 days. 2 weeks later, the liver disease flared up but the CD4 and CD8 counts returned to normal (figure). The nadir of the T cells (CD3) and CD16 cells (100/ μ L) on day 8 correlated with the peak of ALT. During the time of increased ALT, the patient had a normal T-cell ratio in peripheral blood. HCV antibodies tested repeatedly positive after day 50 (Abbott Diagnostics, second generation enzyme-linked immunosorbent assay). Because the patient had normal aminotransferase values but remained HCV-RNA positive for more than 3 months (nested polymerase

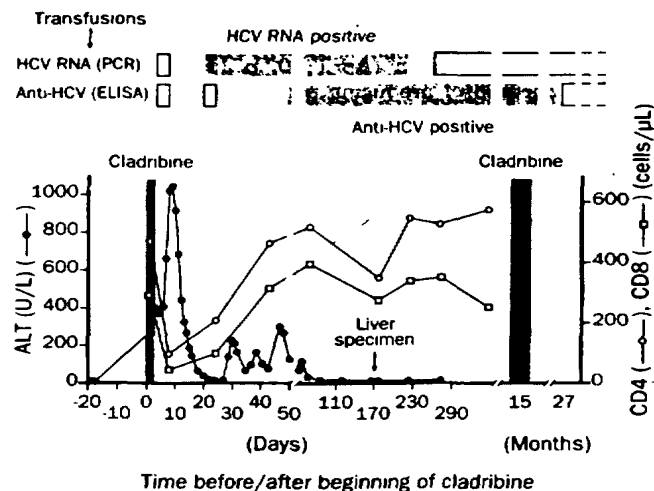


Figure: Clinical course of hepatitis C infection

Open bars indicate negative results and filled bars indicate when serum was positive. Days with cladribine infusions are marked by dark vertical bar.

chain reaction [PCR] primers from the 3' non-coding region), liver biopsy was carried out 5 months after therapy to rule out chronic liver disease. Histology showed normal liver architecture without inflammation, and HCV RNA became undetectable on repeated testing after 9 months.

After 3 months, bone marrow examination showed partial remission with 12% hairy-cell infiltration. However, the number of hairy cells in the bone marrow rose to 20% after 1 year. A course of 7 days' treatment with cladribine (0.1 mg/kg daily) was given without any increase in ALT 15 months after the first course. This second treatment resulted in complete remission of the hairy-cell leukaemia. HCV antibodies were negative 9 months after the second course of cladribine.

This case is remarkable for several reasons. First, a fulminant increase in ALT occurred during cladribine therapy yet had a benign course. During the second course of treatment with cladribine, there was no liver reaction. This, together with seroconversion, would suggest that fulminant hepatitis C and not cladribine, was responsible for the increase in ALT during the first course of cladribine. Second, the rapid return to normal of ALT correlated with marked changes in the number of CD4 and CD8 cells. Third, the patient tested negative for HCV RNA early in the hepatic phase.

Our observations indicate that cladribine may not be detrimental in hepatitis C. The short course of hepatitis C under these conditions could mean either that the reduction in cytotoxic T cells is related to the liver disease, underscoring the role of the immune system in HCV, or that cladribine has some direct antiviral effect. The early negative results for HCV RNA by PCR stress the need for repeated testing in fulminant HCV.

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